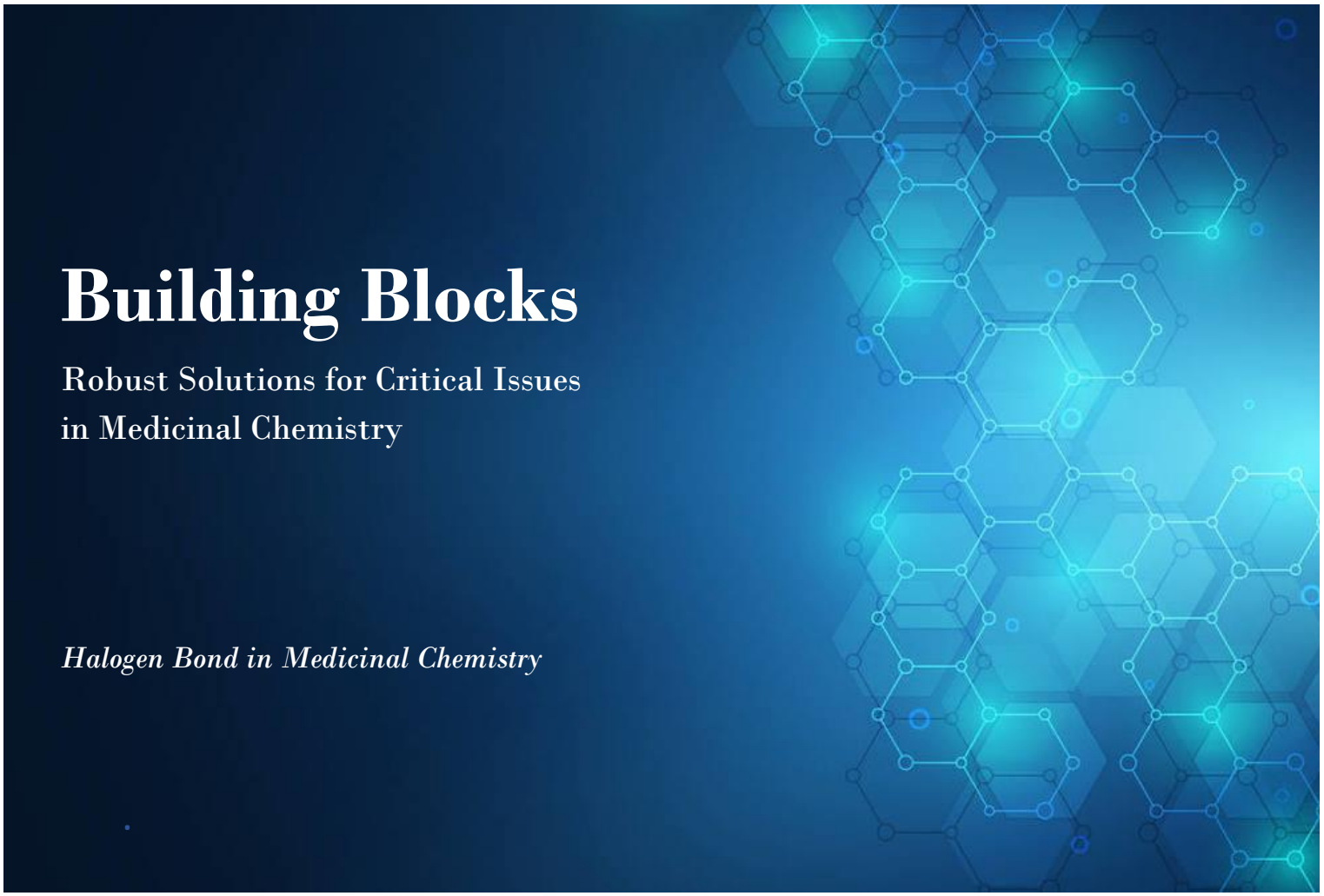
Building Blocks
Robust Solutions for Critical Issues
in Medicinal Chemistry
Halogen Bond in Medicinal Chemistry

Halogen Bond in Medicinal Chemistry

Halogen bond is driven by the σ-hole, a positively charged region on the hind side of chlorine (Cl), bromine (Br) and iodine (I) along the axis of R-Cl, R-Br and R-I bond that is caused by an anisotropy of electron density on the halogen. [1-2] Because of its presence in every amino acid, the backbone C=O is the most prominent acceptor involved in halogen bonds as found from an analysis of PDB. Additionally, halogen bonds can be formed involving protein residues, such as –OH in serine, threonine and tyrosine, -COOH in aspartate and glutamate, -SH in cysteine, -SMe in methionine, N in histidine, and pi-surface of phenylalanine, tyrosine and tryptophan (**Figure 11**). Therefore, this multitude of different interactions possibilities in ligand-protein interactions makes halogen bond a very useful tool to enhance affinity and selectivity.

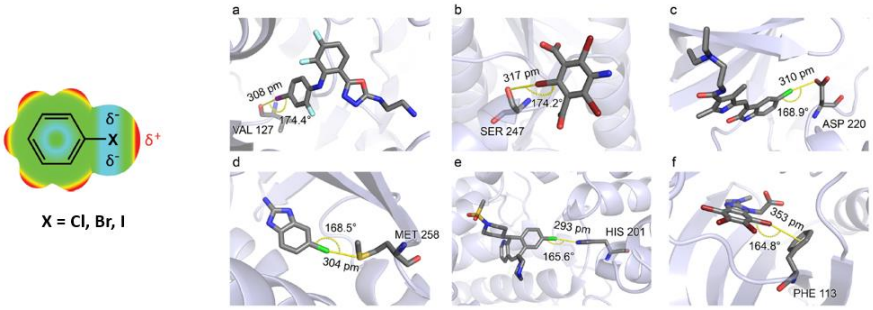

Figure 11. σ-Hole of Cl, Br and I; Different types of halogen bonds in ligand-protein interactions.

It was interesting to observe that a single chlorine in compound **33** increased potency by > 5-fold comparing with analog compound **32**. The same trend was also observed when comparing compound **34** and compound **35** with 20-fold difference in potency caused by a single chlorine. [3] To better understand this observation and further optimize, an X-ray crystal structure of compound **33** bound to HPK1 was obtained. The chlorine atom at the C2 position on compound **33** forms a halogen bond with the gatekeeper Met91, well explaining the reason for potency difference caused by chlorine atoms in compound **33** and compound **35**.

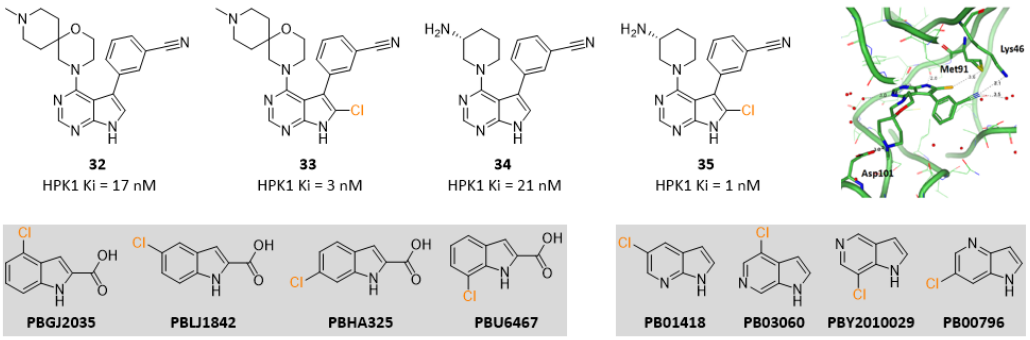

Figure 12. Halogen bond between chlorine and sulfur of Met91 increased potency. (PDB code: 8FH4)

Fragment-based drug discovery (FBDD) has become a standard asset in the search for structurally novel small-molecule therapeutics. Incorporation of halogens into fragments could change their interaction profile significantly based on halogen bond, leading to previously overlooked binding modes to known targets, which could have intrinsic advantages in selectivity. [4] Screening DYRK1a against a halogen-enriched fragment library using an STD-NMR protocol generated fragment hit **36**,

with Kd = 533 uM and a high LE = 0.45. The crystal structure of DYRK1a in complex with fragment **36** was solved. The binding mode in the ATP pocket is dominated by a halogen bond between Br and the backbone C=O of E239 (**Figure 13**). Structure-activity relationship (SAR) insights gained from analogues demonstrated that: 1) removing a nitrogen from triazole increased affinity by > 10-fold (**36** *vs* **37**); 2) the pyridine nitrogen seems to have no significant effect (**37** *vs* **38**). A new fragment-growth vector was established, and incorporation of an acetamide increased the affinity to single-digit 4 uM.

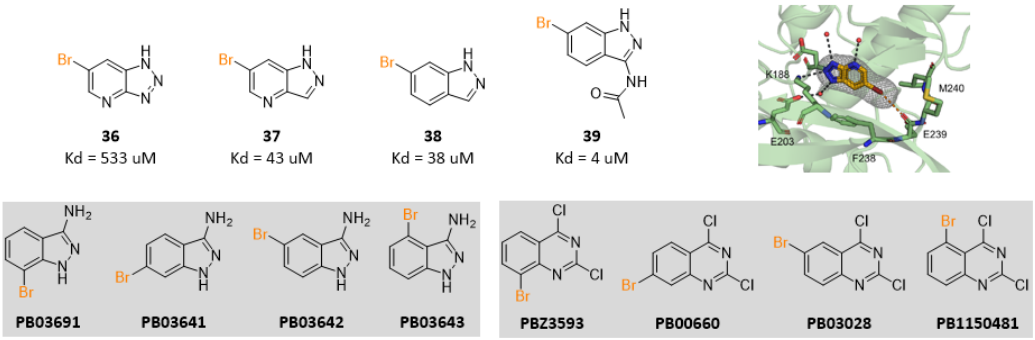

Figure 13. Br of compound **36** forms a halogen bond with the backbone C=O of E239. (PDB code: 7ZH8)

The general trend for the strength order of halogen bond is Cl < Br < I. As exemplified in **Figure 14**, halogen bond between chlorine in compound **41** and the backbone C=O of Phe217 brought 25-fold increased affinity (**40** *vs* **41**). The affinity trend from compound **41** to **43** is consistent with the strength order of halogen bond, although the difference is within 4-fold. [5]

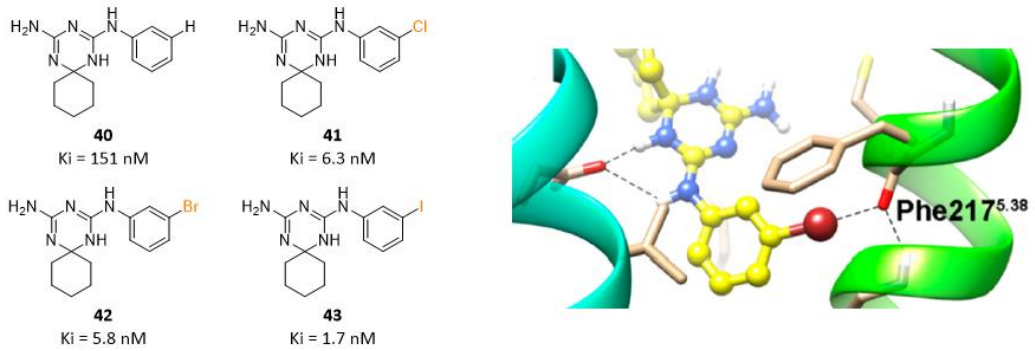

Figure 14. Br of compound 42 forms a halogen bond with the backbone C=O of Phe217.

With possibility of improving the bioactivity by halogen bond in mind, hydrogen atom in compound **44** was replaced by halogen atoms: Cl in compound **45**, Br in compound **46** and I in compound **47** (**Figure 15**). [6] The affinity trend from compound **45** to **47** is also consistent with the strength order of halogen bond. X-ray crystal structures of compound **45** and compound **46** bound to PDE5 were obtained. Both Cl in compound **45** and Br in compound **46** form halogen bonds with O of PDE5 residue Y612, which agrees with observation in affinity increasing.

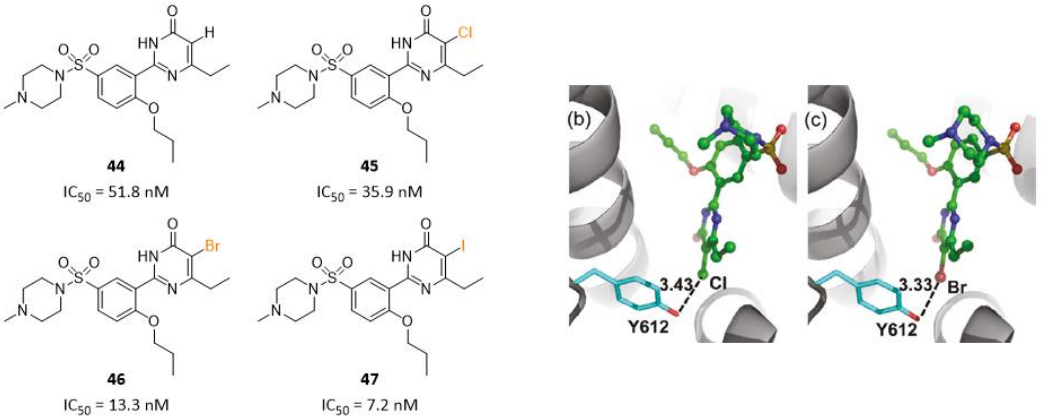

Figure 15. Halogen bonds between Cl or Br and O of PDE5 residue Y612.

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